A Phase I Pharmacokinetic and Pharmacodynamic Study of TKI258, an Oral, Multitargeted Receptor Tyrosine Kinase Inhibitor in Patients with Advanced Solid Tumors

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Abstract

Purpose: To determine the maximum tolerated dose (MTD) dose-limiting toxicity, and pharmacokinetic and pharmacodynamic profile of TKI258 (formerly CHIR-258).

Experimental Design: A phase I dose escalating trial in patients with advanced solid tumors was performed. Treatment was initially as single daily doses on an intermittent 7-day on/7-day off schedule. Following a protocol amendment, a second schedule comprised, during cycle 1, 7-day on/7-day off treatment followed by 14 days of continuous daily dosing; subsequent cycles comprised 28 days of daily dosing. Pharmacokinetics and evaluation of phosphorylated extracellular signal-regulated kinase (ERK) in peripheral blood mononuclear cells were done during the first 28 days of each schedule.

Results: Thirty-five patients were treated in four intermittent (25-100 mg/d) and three continuous (100-175 mg/d) dosing cohorts. Observed drug-related toxicities were nausea and vomiting, fatigue, headache, anorexia, and diarrhea. Dose-limiting toxicities were grade 3 hypertension in one patient at 100 mg continuous dosing, grade 3 anorexia in a second patient at 175 mg, and grade 3 alkaline phosphatase elevation in a third patient at 175 mg. One patient had a partial response (melanoma) and two patients had stable disease >6 months. TKI258 pharmacokinetics were linear over the dose range of 25 to 175 mg. Five of 14 evaluable patients had modulation of phosphorylated ERK levels.

Conclusions: The MTD was defined as 125 mg/d. Evidence of antitumor activity in melanoma and gastrointestinal stromal tumors warrants further investigation, and other phase I studies are ongoing. Further pharmacodynamic evaluation is required in these studies to evaluate the biological effects of TKI258.

TKI258 is an oral multitargeted receptor tyrosine kinase (RTK) inhibitor. The development of RTK inhibitors for the treatment of cancer has provided significant therapeutic advances for a range of malignancies. In particular, drugs targeting the vascular endothelial growth factor receptors (VEGFR) have shown considerable promise (e.g., sunitinib and sorafenib for renal cancer; refs. 1, 2). TKI258 has shown direct activity against tumor cells and the formation and maintenance of blood vessels and stroma supporting tumors. TKI258 is a potent inhibitor of the class III, IV, and V RTKs, showing biochemical IC50 values <20 nmol/L for VEGFRs (VEGFR-1, VEGFR-2, and VEGFR-3); the platelet-derived growth factor receptor-β (PDGFR-β); fibroblast growth factor receptors 1, 2, and 3 (FGFR-1, 2, 3); fetal liver tyrosine kinase receptor 3 (FLT-3); and KIT Ret, TrkA, and csf-1 RTKs (3). Although the principal targets of TKI258 are the VEGF RTKs, the unique inhibition profile of TKI258 differentiates it from several other RTK inhibitors; in particular, as it significantly inhibits the fibroblast growth factor receptors, TKI258 shows significant activity in a variety of tumor xenograft models in athymic mice, including acute myeloid leukemia, multiple myeloma, and colon- and prostate-derived models. Those xenografts using cell lines driven by activating mutations or ectopic expression of target RTKs were particularly sensitive to the effects of TKI258 (3).

TKI258 shows a dose- and exposure-dependent inhibition of target RTKs expressed in tumor xenografts and stromal components in several preclinical models. Inhibition of RTK phosphorylation was maintained for 24 h after a single dose of TKI258, with corresponding inhibition of downstream signaling pathways as measured by the inhibition of phosphorylation of extracellular signal-regulated kinase (ERK) and AKT. TKI258
efficacy in tumor models is correlated with inhibition of these
downstream signaling pathways, inhibition of proliferation,
reduction in tumor microvessel density, and induction of
apoptosis, depending on the tumor model and target RTKs
expressed (4). Studies with TKI258 in isolated human and rat
peripheral blood mononuclear cells (PBMC) showed dose-
dependent inhibition of phosphorylated ERK (phospho-ERK)
using both flow cytometry and Western blotting.

Preliminary pharmacokinetic studies showed good oral
bioavailability, with moderate-to-high plasma clearance and
large volume of distribution (\(V_{ss}\)). Plasma half-life was
adequate for once daily dosing in tumor models, and plasma
exposure increased proportionally with dose. Given the highly
promising preclinical antitumor activity and safety data in
animals, this phase I first-in-human study of oral TKI258
was undertaken to determine the maximum tolerated dose,
dose-limiting toxicities (DLT), and safety profile of TKI258, together
with pharmacokinetic and pharmacodynamic analyses, when
administered to patients with advanced solid malignancies. A
secondary objective was to describe antitumor activity.

Materials and Methods

Eligible patients were recruited from two centers in the United
Kingdom: The Royal Marsden Hospital/Institute of Cancer Research
(Sutton) and The Beatson Oncology Centre (Glasgow). The study,
sponsored by Novartis (Chiron Corp.), was approved by the Local
Research Ethics Committees of both institutions and conducted in
accordance with the principles of the Declaration of Helsinki and
International Conference on Harmonization Guidelines for Good
Clinical Practice. All patients gave written informed consent before
any study-related procedures were done.

Patient eligibility. Patients with histologic or cytologic confirmation
of locally advanced or metastatic solid tumors who were refractory or
resistant to conventional therapy or for which no standard therapy
exists were eligible provided they met the following criteria: age of
\(\geq 18\) years; Eastern Cooperative Oncology Group (ECOG) performance
status of 0 to 1; anticipated survival of \(\geq 12\) weeks; evidence of
measurable or evaluable disease; adequate hematopoietic (absolute
neutrophil count \(\geq 1.5 \times 10^9\) L, platelet count \(\geq 75 \times 10^9\) L,
hemoglobin \(\geq 8\) g/dL), hepatic [bilirubin \(\leq 1.5 \times \) upper limit of normal
(UlN)], alkaline phosphatase \(\leq 5 \times UlN\), aspartate aminotransferase
\(\leq 2.5 \times UlN\) (or \(\leq 5 \times UlN\) in the presence of liver metastases), amylase
(\(\leq UlN\)), and renal (serum creatinine \(\leq 1.5 \times UlN\) function; were
\(\geq 21\) days since the last dose of antineoplastic therapy (prostate cancer
patients could continue luteinizing hormone-releasing hormone
analogue therapy); and a negative pregnancy test for females of
childbearing potential.

Exclusion criteria included the following: concurrent therapy with
another investigational agent, concurrent active intracranial or epidural
metastases, pregnancy or lactation, clinically significant cardiac disease,
grade \(\geq 2\) compromised left ventricular ejection fraction (LVEF),
diabetes mellitus requiring chronic medication, pericarditis or clinically
significant pleural effusion in the previous 12 months, malabsorption,
prior pancreatitis, prior intrahepatic or extrahepatic biliary obstruction

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Fig. 1. Treatment schema for intermittent and continuous dosing schedules of TKI258. Shaded boxes, "on drug" days; unshaded boxes, "off drug" days. For the intermittent schedule, DLT was defined as occurring in the first 28 d (cycle 1). For the continuous schedule, DLT was defined as occurring in the 7-d/7-d off intermittent lead-in period and the first 14 d of continuous dosing.
within the previous 12 months, or history of malignant obstruction requiring biliary stent unless stably treated with no prior obstruction or blockage of stent.

**Drug administration.** TKI258 was supplied as a 1 or 5 g crystalline powder in a bottle. Sufficient water for irrigation was added to make a final concentration of 10 to 50 mg/mL. Seven to 16 individual bottles were dispensed at a time. For the initial 7 days of dosing, TKI258 was ingested either 1 h before a meal or 2 h following a meal; thereafter, ingestion was with food. Patients could add one to two tablespoons of water or clear fruit juice (except grapefruit juice) to the bottle to swallow any remaining content. The constituted solution was stored at 2°C to 8°C and used within 28 days. Appropriate supportive therapies were permitted.

**Study design.** Patients were assigned to receive escalating doses of TKI258 once daily in two schedules (Fig. 1). Initially, all patients received TKI258, on an intermittent lead-in period, on days 1 to 7 followed by 7 days off drug. Thereafter, patients were treated in two sequential groups. In the first group, patients continued on an intermittent schedule every 28 days (one cycle). Doses of 25 to 200 mg were planned. Once initial drug safety and pharmacokinetic data had been acquired, the second group of patients received 7-day on/7-day off treatment followed by continuous daily dosing; doses of 100 to 235 mg were planned. At least three patients were treated at each dose level.

**Dose escalation procedure and definition of DLT and maximum tolerated dose.** Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3. Doses were escalated by doubling until the first drug-related grade 2 toxicity was observed. Thereafter, a modified Fibonacci schema was used (dosing increments of 50%, 40%, 33%, and 25%).

DLT was defined as any of the following determined possibly or probably related to TKI258 and occurring during the first 28 days of therapy for both schedules: grade 4 neutropenia for >5 days or febrile neutropenia (fever ≥38.5°C with grade 3 or 4 neutropenia); grade 4 thrombocytopenia or grade 3/4 thrombocytopenia with bleeding requiring platelet transfusion; grade 4 fatigue or two-point decline in ECOG performance status; grade ≥3 nausea, vomiting, diarrhea, and/or myalgia despite maximal medical intervention; grade ≥3 nonhematologic toxicity except fatigue; persistent grade 3 hypertension despite appropriate therapy; and grade ≥2 cardiac toxicity and treatment delay of >2 weeks due to delayed recovery from TKI258-related toxicity.

If there were no DLTs in the first three patients at each dose level, dose escalation proceeded. If one of three patients experienced a DLT, an additional three patients were treated at the same dose level. If no further DLTs were observed, dose escalation proceeded. However, if a further DLT (two of up to six patients) was observed, the maximum tolerated dose was exceeded and the preceding dose level would be the recommended dose.

**Dose modification.** If patients experienced absolute neutrophil count <1.0 × 109 L, hemoglobin <8 g/dL, and platelets <75 × 109 L, dosing was delayed until recovery of these values. If toxicities persisted for >21 days after detection, study treatment was discontinued. Dose reduction by one level was permitted for significant toxicities possibly or probably related to TKI258. Only one further dose reduction (but not <25 mg) was allowed if drug toxicity persisted.

**Study procedures.** A full history and physical examination was carried out before study entry and at the start of each 28-day cycle. Clinical evaluation of vital signs and monitoring of adverse events and complete blood count and serum biochemistry and electrolytes were done before study entry and weekly during treatment. Electrocardiograms were done weekly and before and 4 h after dose during the lead-in period and before each 28-day cycle. Cardiac assessment with a multigated acquisition scan or echocardiogram was done at study entry and after every two cycles. Disease was assessed according to Response Evaluation Criteria in Solid Tumors using computed tomography and/or magnetic resonance imaging scans at study entry and following every two cycles thereafter until discontinuation from the study. Tumor markers were assessed at each cycle as appropriate. Radiologic responses were confirmed by repeat imaging done after an interval of at least 28 days. Patients continued treatment provided they did not experience progressive disease or unacceptable drug-related toxicity.

**Pharmacokinetic sampling and assay.** During the initial intermittent lead-in period, on days 1 and 7, 7 mL blood samples were taken before drug ingestion and 2, 3, 4, 5, 6, 8, 10-16, and 24 h after ingestion. A 48-h sample was taken after day 7 dosing only. For those patients continuing on the intermittent schedule, repeat pharmacokinetic sampling over a 24-h period was done on days 15 and 16 of cycle 1. This 24-h sampling schedule was also repeated in patients on the continuous schedule at days 1 and 15, 16 and either days 26, 27, or 28 of cycle 1. Plasma was separated from blood samples and stored frozen at -70°C until analysis. The cell pellet underwent RBC lysis and the cells were also frozen at -70°C until analysis. Plasma samples were analyzed for unchanged TKI258 concentrations and metabolites of TKI258. The following pharmacokinetic variables were evaluated from the plasma samples by noncomparitional analyses: half-life, maximum concentration (Cmax), and area under the curve. Concentration of TKI258 in plasma was quantitated with a high-performance liquid chromatography assay.

**Pharmacodynamic and genotyping sampling.** Serial blood sampling was done in the first two cycles for pharmacodynamic analyses. In the intermittent lead-in period, samples were taken before dose and 4 and 24 h after dose on days 1, 2, and 7. Further samples were taken at the same time points on days 15 and 16 of both schedules and either days 26, 27, or 28 of the continuous schedule. Plasma levels of circulating VEGF and VEGFR were measured by ELISA at the above blood sampling time points; samples were collected in 5 mL EDTA tubes. PBMCs were isolated from sodium heparin samples for Western blot analysis. PBMCs were analyzed for inhibition of ERK phosphorylation using phospho-p44/42 mitogen-activated protein kinase (MEK) inhibitor CP-690,550.

**Table 1. Baseline characteristics**

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<th>Characteristics</th>
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<td>Patients</td>
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<td>Male</td>
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<td>Median age, y (range)</td>
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<td>&gt;6</td>
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<td>CRC</td>
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<td>GIST</td>
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<td>Sarcoma</td>
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<td>Other*</td>
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**Abbreviations:** PS, performance status; CRC, colorectal; GIST, gastrointestinal stromal tumor.

*Other: breast, parotid, carcinoma unknown primary, dermatofibrosarcoma protuberosans, sinonasal neuroendocrine tumor, ovarian, and nasopharyngeal.
protein kinase (Thr^{202}/Tyr^{204}) and total p44/42 mitogen-activated protein kinase antibodies (Cell Signaling) to determine the degree to which TKI258 blocked intracellular signaling in PBMCs.

**Results**

Thirty-five patients were recruited (20 male and 15 female) between December 2003 and November 2005, with a median age of 56 years (range, 30-71). Patient characteristics are listed in Table 1.

No DLT was observed during the first four dose cohorts of the intermittent schedule. Three DLTs were observed with the continuous dosing schedule: one at 100 mg/d and two at 175 mg/d. At 100 mg/d, one patient with preexisting hypertension developed grade 3 hypertension (see below). At 175 mg/d, one patient with metastatic duodenal carcinoma had an asymptomatic grade 3 rise in serum alkaline phosphatase (with no other significant biochemical abnormalities), which resolved on discontinuation of study drug; another patient with advanced nasopharyngeal carcinoma experienced both grade 3 anorexia (and grade 3 fatigue) attributable to drug. The maximum tolerated dose of TKI258 was therefore determined to be 125 mg/d continuous dosing and seven patients in total were treated at this dose level.

Table 2 shows the number of patients experiencing clinical adverse events grade ≥2 regardless of relationship to study drug. The drug was generally well tolerated. There was no evidence of any significant hematologic or renal toxicity. Fatigue and gastrointestinal toxicities (nausea, vomiting, anorexia, and diarrhea) were the most common adverse events (Table 2). Grade 2 fatigue occurred in 8 of 35 (23%) patients and grade 3 to 4 in 3 patients. Patients on the intermittent schedule had resolution of fatigue during the washout period. With the continuous dosing schedule, fatigue was not cumulative. Nausea and vomiting were usually self-limiting and easily managed with standard antiemetics (5-hydroxy-3 receptor antagonists were never required). Diarrhea was similarly easily managed.

Cardiovascular events were seen in five (14%) patients. Hypertension was observed in two patients at 100 mg continuous dosing. One patient with hormone-refractory prostate cancer and preexisting hypertension (on doxazosin monotherapy) developed grade 3 hypertension during the first cycle of treatment requiring addition ofamlodipine and an increase in the dose of doxazosin. TKI258 dosage was interrupted for 1 week followed by reduction in dose to 100 mg intermittent dosing. Subsequent blood pressure readings returned to pretreatment levels, with no further exacerbations on redosing.

A second patient with familial von Hippel Lindau syndrome and renal cell carcinoma developed uncomplicated grade 2 hypertension during the second cycle of treatment and required

<table>
<thead>
<tr>
<th>Table 2. Clinical adverse events</th>
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<tr>
<td><strong>Adverse event</strong></td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Anorexia</td>
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<td>Reduced LVEF</td>
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<td>Hypertension</td>
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<tr>
<td>Pulmonary embolism</td>
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<tr>
<td>Troponin I increase</td>
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<td>ALP elevation</td>
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Abbreviation: ALP, alkaline phosphatase. *Continuous schedule.
the addition of an antihypertensive (atenolol). The dose of TKI258 was reduced to 100 mg intermittent dosing, with full resolution of hypertension.

Grade 2 declines in LVEF were noted in two patients on the intermittent schedule. In both patients, the relationship to study drug was unclear. One patient with metastatic gastrointestinal stromal tumor had a preexisting history of hypertension and cerebrovascular disease but no known ischemic heart disease. This patient developed a progressive fall in LVEF (baseline, 69%; at 2 months, 55%; at 6 months 50%) as noted by multigated acquisition scan during 7 months on TKI258, ultimately developing symptomatic heart failure requiring treatment.

A second patient with metastatic renal cell cancer developed an asymptomatic grade 2 fall in LVEF during 4 months on TKI258. Multigated acquisition scan LVEF at baseline was 63%, at 2 months was 54%, and at 4 months (end of study) was 47%. Echocardiography showed no structural abnormality and LVEF recovered to baseline following end of treatment.

In addition, one patient with metastatic ovarian cancer developed asymptomatic grade 3 elevation in cardiac troponin I. She had no previous cardiac history or risk factors. The troponin I rise occurred after 1 month of treatment but was not associated with any symptoms or electrocardiogram changes. Given the degree of rise, TKI258 was discontinued. She then had a rapid fall in troponin I levels. Subsequent echocardiogram showed no significant abnormalities. The underlying cause of the troponin I rise may also have been related to the development of a pulmonary embolism shortly after stopping TKI258; hence, the relationship with TKI258 treatment was unclear.

**Pharmacokinetics.** The plasma pharmacokinetics of TKI258 was dose proportional over the dose range of 25 to 175 mg (see Fig. 2). Preliminary analyses across this dose range indicated that, on day 1, the mean $C_{\text{max}}$ was 13.5 ($\pm$ 5.3) ng/mL to 103.2 ($\pm$ 26) ng/mL and the mean area under the curve (0-24 h) was 244 ($\pm$ 110.6) ng*h/mL to 1,626.5 ($\pm$ 500.7) ng*h/mL, with an average half-life of ~17 h. For the first four dosing cohorts on the intermittent schedule, plasma exposures were lower on day 7 compared with day 1. This time-dependent reduction in pharmacokinetics seemed to reverse after 7-day washout.

Trough TKI258 concentrations at all doses >50 mg/d were above the concentrations known to inhibit target receptor activation in vitro. In target-driven mouse xenograft models, dose levels associated with efficacy were between 10 and 30 mg/kg (3). $C_{\text{max}}$ in these models at these dose levels was in the range of 123 to 952 ng/mL, and area under the curve was 1,420 to 9,570 ng*h/mL. Although the exposure in this clinical study is therefore less, it is difficult to compare the clinical and preclinical pharmacokinetic data as it is not known what drives activity (e.g., $C_{\text{min}}, C_{\text{max}}$ or area under the curve).

**Pharmacodynamics.** To determine if TKI258 affects ERK activation in PBMCs, blood from normal donors was treated ex vivo with TKI258. No exogenous stimulation (e.g., with phytohemagglutinin) was done. Dose-dependent inhibition in endogenous phospho-ERK was observed by Western blot and flow cytometry assays after incubation of PBMCs with TKI258. This assay was therefore used to evaluate target modulation after oral dosing to confirm biological activity in the patient population.

In 14 of 35 patients, there were adequate quantities of PBMCs and adequate pretreatment signal of phospho-ERK for pharmacodynamic analyses. Five of 14 patients showed modulation of phospho-ERK, with strong inhibition of signal as measured by Western blotting on day 1, 4 h after dose, with inhibition maintained on days 7 and 15 at 4 and 24 h after dose (see Fig. 3). There was no clear dose or exposure correlation with extent or duration of modulation. Individual subject plasma VEGF and soluble VEGFR-2 showed no consistent effects through all dose cohorts. Other growth factors (fibroblast growth factor, placenta growth factor, stem cell factor, fms-like tyrosine kinase receptor 3 ligand, and intercellular adhesion molecule-1) and soluble receptors were examined in plasma but showed no consistent effects or trends.

**Antitumor effects.** One patient with melanoma achieved a partial response and remains on TKI258 at 175 mg (started on TKI258, September 2005; see Fig. 4). Stable disease as best overall response was reported in 9 of 35 (25.7%) patients. Two
of these patients had stable disease >6 months (gastrointestinal stromal tumor, 8 months; parotid tumor, 7 months), whilst four had stable disease >4 months (two patients with renal cell carcinoma, 4 and 5 months, respectively; prostate cancer, 5 months; esophageal cancer, 5 months).

The patient with imatinib-refractory gastrointestinal stromal tumor (and had also received sorafenib) who showed stable disease with TKI258 was treated with 75 mg/d on the intermittent schedule for 8 months. Positron emission tomography scans showed that TKI258 resulted in reduced fluoro-2-deoxyglucose uptake in tumor during therapy, which was associated with significant symptomatic improvement.

### Discussion

In this first-in-man study of the multitargeted RTK inhibitor TKI258 in patients with advanced solid tumors, DLTs of hypertension, fatigue, anorexia, and elevation of alkaline phosphatase were determined. Overall, treatment was well tolerated at the dose levels studied; the most common adverse events seen were mild-to-moderate fatigue, nausea, vomiting, and diarrhea. This adverse event profile was similar to that already seen with other multitargeted RTK inhibitors (5–7). Hypertension was observed in this study and seems to be a class effect for agents targeting VEGFR. However, this occurred in only a minority of patients (2 of 35), was easily manageable with antihypertensive therapy, and did not preclude chronic dosing.

Fatigue, nausea, diarrhea, and anorexia have also been reported with small-molecule RTK inhibitors. Interestingly, treatment with TKI258 did not lead to the debilitating fatigue often seen with sunitinib, or significant rash or hand-foot syndrome, as commonly seen with both sorafenib and sunitinib (5, 6). In addition, there was no evidence of lightheadedness or dizziness, the DLT for vatalanib (7). In addition to hypertension, reduction in LVEF was reported in two patients; relationship of this to TKI258 was unclear. The maximum tolerated dose was defined as 125 mg/d based on the DLTs at 175 mg/d and evidence of target modulation. However, although further dose escalation was halted at the 175 mg/d dose level in this study, this may not be the highest safe clinically administrable dose based on data from ongoing phase I studies of TKI258 in hematologic malignancies and melanoma. This may be because of underlying differences in these patient populations (e.g., age, differences in pharmacokinetics, and biology of the underlying tumor), and further data are awaited with interest.

In this study, the modulation of phosphorylated ERK in PBMCs and measurement of growth factors and soluble receptors were used as surrogate pharmacodynamic biomarkers to assess biological activity with TKI258. To date, there have been no validated biomarkers (of either proof of concept or prediction of response) for agents targeting VEGF. Functional imaging with dynamic contrast-enhanced magnetic resonance imaging and computed tomography have been the most commonly used techniques to date (8–10). Although they have shown promise, there are several limitations with these techniques. These relate to both the high heterogeneity of blood flow and the measurement of composite variables, which depend on both blood flow and permeability (11), resulting in significant intrapatient and interpatient variability. This results in only large changes in blood flow, reflecting vascularity, and permeability, reflecting VEGFR inhibition, being reliably measurable. The use of blood or urine to measure proteins as surrogate markers in patients with solid tumors where access to tumor tissue can be difficult is promising (12, 13). ERK phosphorylation is a well-characterized downstream effect of RTK activation, and in vitro, TKI258 modulated phospho-ERK in tumor and endothelial cells (possibly through either VEGFR or KIT). However, in this study, the use of phospho-ERK in PBMCs was hampered by absent or low signal in the majority of patients. Five of 14 evaluable patients showed modulation of phospho-ERK. These patients did not have corresponding changes in serum VEGF or soluble VEGFR; in fact, there were no significant changes in growth factors or soluble receptors in any patients. The significance of these results is unclear. It seems that measurement of phospho-ERK in peripheral blood lymphocytes by Western blotting does not have sufficient reliability to be used as a successful biomarker at present. The use of serum VEGF and soluble VEGFR-2 potentially holds more promise, as was shown in the phase I study of sunitinib in patients with solid tumors: increase in VEGF and reduction in serum VEGFR-2 was felt to represent adequate dosage. In the future, techniques likely to be explored include the detection of circulating endothelial, progenitor, or tumor cells (14, 15); combining and comparing multiple variables will need to be done in phase I to II trials of new VEGF targeting agents to properly define the effects of these drugs and to identify meaningful surrogate markers of activity and efficacy.

Antitumor activity was observed in a patient with metastatic melanoma and one with imatinib-refractory gastrointestinal stromal tumor. This is encouraging because these tumors are difficult to treat, and further testing in these tumor types may be warranted.

In conclusion, TKI258 shows an acceptable safety profile for patients with advanced solid tumors at doses up to 125 mg/d. Evidence of antitumor activity was seen in patients with a range of tumor types. Further studies evaluating the safety profile and efficacy of TKI258 are ongoing.

### References

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